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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,289	06/16/2005	Gera Neufeld	29432	5166

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
11/06/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,289	NEUFELD, GERA	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-23* is/are pending in the application.

4a) Of the above claim(s) *4-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1 and 4-23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 7/23/08 has been entered in full. Claim 1 is amended. Claims 2 and 3 are canceled.

Claims 1 and 4-23 are pending.

Claims 4-23 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim 1 is under consideration.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (1/23/08).

The objection to the specification at pg 2 is *withdrawn* in view of Applicants' amendments to the specification.

All objections and/or rejections of claims 2 and 3 are moot in view of Applicants' cancellation of these claims.

The rejection of claim 1 under 35 U.S.C § 112, second paragraph, at pg 3 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claim.

The rejection of claim 1 under 35 U.S.C. § 112, first paragraph at pg 3-8 for failing to provide enablement for the full scope of the claim is *withdrawn* in view of Applicants' amendments to the claim.

The rejection of claim 1 under 35 U.S.C. § 112, first paragraph at pg 8-10 for failing to comply with the written description requirement is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claim 1 under 35 U.S.C. § 102(b) as anticipated by Li et al (2000) is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claim 1 under 35 U.S.C. § 102(b) as anticipated by Cunningham et al (WO 00/63380) is *withdrawn* in view of Applicants' amendments to the claims.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al, WO 00/63380 (published 10/26/00; cited previously) in view of Poltorak et al, 1997 (Journal of Biological Chemistry. 272(11): 7151-7158; cited previously). This rejection was set forth at page 12-14 of the 1/23/08 Office Action.

For clarity, the rejection is first restated in view of Applicants' amendments to the claims, and then Applicants' arguments are addressed.

Amended claim 1 is limited to a previously encompassed embodiment; specifically, an isolated $VEGF_{145}$ polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 4. This particular embodiment was the basis of the rejection of claim 1 set forth previously under 103(a). The instant specification teaches that SEQ ID NO: 4 has three point mutations (Arg-63-Ser; Gly-64-Met; and Leu-66-Arg) as compared with the "wildtype" $VEGF_{145}$ sequence (SEQ ID NO: 3).

Cunningham teaches a mutant $VEGF_{109}$ polypeptide ("LK-VRB-2s") and a mutant $VEGF_{165}$ sequence ("LK-VRB-2f"), each with three point mutations: Arg-63-Ser; Gly-64-Met; and Leu-66-Arg (see pg 30, line 26 through pg 31, line 5 and Table 2). Table 6 (pg 37) shows these two variants can each bind the KDR receptor but have greatly reduced FLT-1 [VEGFR-1] binding activity. Cunningham further teaches that the term "VEGF" as used therein refers to the "the 165- amino acid vascular endothelial growth factor and related 121-, 189- and 206- amino acid vascular endothelial cell growth factors... together with the naturally occurring allelic and processed forms thereof" (pg 8, line 6-11) and to "truncated forms of the polypeptide comprising amino acids 8 to 109 or 1 to 109 of the 165-amino acid vascular endothelial growth factor" (pg 8, lines 12-14).

Cunningham further teaches that "[p]referred VEGF variants have one or more amino acid substitutions at positions 63, 65 and/or 66 of VEGF, wherein the amino acid residue at position 63 is substituted with serine, the amino acid residue glycine at position 65 is substituted with methionine, and/or the amino acid residue leucine at position 66 is substituted with arginine" (pg 4, line 43 to pg 5, line 4). Cunningham further teaches that VEGF variants include those with amino acid deletions (pg 11, line 36) and that such deletions "generally range from about 1 to 30 residues, more preferably 1 to 10 residues, and typically are contiguous" (pg 12, lines 19-20). Cunningham further teaches that "[p]referred VEGF variants of the invention will additionally or alternatively induce endothelial cell proliferation (which can be determined by known art methods such as the HUVEC proliferation assay in the Examples)" (pg 14, lines 1-4). Cunningham does not teach a wildtype or mutated VEGF sequence with 145 amino acids.

Poltorak teaches that $VEGF_{145}$ is a splice variant of VEGF consisting of 145 amino acids; other known splice variants consist of 121, 165 or 189 amino acids. Poltorak teaches that the $VEGF_{145}$ form lacks exon 6 (as opposed to $VEGF_{165}$, which lacks exon 7), but "the domain encoded by exons 1-5 contains information required for the recognition of the known VEGF receptors KDR/*flk-1* [aka VEGFR-2] and *flt-1* [aka VEGFR-1]… and is present in all VEGF isoforms" (pg 7151). Poltorak further teaches that "$VEGF_{145}$ was found to induce endothelial cell proliferation and in vivo angiogenesis, in agreement with previous studies that have indicated that these functions are not dependent on the presence of either exon 6 or exon 7" (pg 7156).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make the amino acid sequence of SEQ ID NO: 4 by making the mutations taught by Cunningham (to residues 63, 65 and 66) in the $VEGF_{145}$ sequence taught by Poltorak. The person of ordinary skill in the art would be motivated to do so because (1) $VEGF_{145}$ meets the definitions of a "processed" or "deleted" VEGF variant as suggested for use by Cunningham as part of the KDR-selective VEGF of the invention and (2) in the absence of other evidence, the mutated $VEGF_{145}$ sequence could used for endothelial cell proliferation as well as the mutated $VEGF_{165}$ taught by

Cunningham. Further, a person of ordinary skill in the art would have had a reasonable expectation of success because producing mutated proteins is routine in the art.

Applicants' arguments (7/23/08; pg 9-11) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the wild type $VEGF_{145}$ polypeptide includes additional sequences (specifically, exon 6a) as compared to the wild type $VEGF_{165}$ polypeptide, and therefore "does meet the definition of a "processed" or "deleted" form of $VEGF_{165}$ (pg 9). Applicants further argue that $VEGF_{145}$ includes exon 6a but lacks exon 7, and $VEGF_{165}$ includes exon 7 and lacks exon 6a. Applicants point out that exon 7 contains 7 cysteine residues not found in exon 6a, increasing the total number of cysteine residues in the protein from 9 to 16. Applicants argue that "since cystein residues can form intra or inter di-sulfide (S-S) bonds in the mature protein, presence or absence of such residues affect the protein secondary and tertiary structure" (pg 10) and that because of the different secondary and tertiary structures, the skilled artisan would not have had a reasonable expectation of success of introducing the mutations of Cunningham et al into $VEGF_{145}$.

Applicants' arguments have been fully considered but are not found persuasive. It is acknowledged that $VEGF_{145}$ includes exon 6a but not exon 7, and $VEGF_{165}$ includes exon 7 but not exon 6a. This is clearly shown in Figure 1A (pg 7153) of Poltorak. However, the definition of "VEGF" taught by Cunningham is not limited to "processed forms" of $VEGF_{165}$, but also includes "processed forms" of $VEGF_{121}$, $VEGF_{189}$, and $VEGF_{206}$. As shown in Figure 1A of Poltorak, the $VEGF_{206}$ form of the protein includes all of the exons (including both 6a and 7). Poltorak teaches that "[t]he human VEGF isoforms are generated by alternative splicing from a single gene" (pg 7151). Thus, even if $VEGF_{145}$ is not considered a processed form of $VEGF_{165}$, it would be considered a processed form of the full-length $VEGF_{206}$. Furthermore, as shown in Figure 1a, $VEGF_{145}$ has 63 amino acids deleted with respect to the sequence of $VEGF_{206}$, and 44 amino acids deleted with respect to the sequence of $VEGF_{189}$. Thus, $VEGF_{145}$ also meets the definition of a "deleted" VEGF variant. Thus, it is maintained that $VEGF_{145}$

meets the definitions of a "processed" or "deleted" VEGF variant as suggested for use by Cunningham as part of the KDR-selective VEGF of the invention.

It is further acknowledged that exon 7 of $VEGF_{165}$ contains seven cysteine residues that would not be found in $VEGF_{145}$ as it lacks this exon. However, the $VEGF_{121}$ form taught by each of Cunningham and Poltorak is also missing exon 7 (as shown in Figure 1A of Poltorak), and this form binds to both KDR/*flk-1* (VEGFR-2) and *flt-1* (VEGFR-1). As Poltorak teaches on page 7156, "...both KDR/*flk-1* and *flt-1* are recognized by $VEGF_{121}$". Poltorak further teaches that "the domain encoded by exons 1-5 contains information required for the recognition of the known VEGF receptors KDR/*flk-1* [aka VEGFR-2] and *flt-1* [aka VEGFR-1]… and is present in all VEGF isoforms" (pg 7151) and that "$VEGF_{145}$ behaves like VEGF121 with regard to its receptor recognition ability" (pg 7151). Furthermore, the only difference in sequence between $VEGF_{121}$ and $VEGF_{145}$ is in exon 6a, which is present in $VEGF_{145}$ but contains no cysteine residues (as shown by Applicants on page 10 of their response). Therefore, there is no evidence that removal of the cysteines of exon 7 would alter the functionality of a VEGF variant with respect to interaction with the VEGFR-1 or VEGFR-2 receptors. Thus, the skilled artisan would not reasonably expect that removing the cysteines of exon 7 would impact the proteins functionality with respect to interaction with the VEGFR-1 or VEGFR-2 receptors, as the $VEGF_{121}$ variant is also missing those cysteines and retains this functionality.

Conclusion

The claim is not allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646